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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,475	06/04/2001	Christos J. Petropoulos	2793/65166/JPW/JML/CMR	5338

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/874,475	PETROPOULOS ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-71,73-76 and 78-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-71, 73-76, 78-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the international Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed December 1, 2004 in response to the Office Action of June 1, 2004 is acknowledged and has been entered. Claims 38-71, 73-76 and 78-94 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The rejection of claims 38-71, 73-76 and 78-94 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is maintained** for reasons of record.

Applicants response indicates that the term "plurality" is intended to encompass both definition of the term identified as being a problem in the previous Office action. Definition 1: "plurality" is interpreted as being more than one of a different kind (for example different envelope structures or different virus structures; in other words different species). Definition 2: "plurality" is interpreted as being more than one of the same kind (for example multiple of the same envelope structures or multiple of the same virus structure). What makes the definition indefinite in the context of the claim is that it is not clear when merely multiple of the same kind are contemplated or multiples of different kinds are contemplated in the claim.

The rejection of claims 38-71 and 73-88 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is withdrawn** in view of Applicants

argument. Applicants' argument is that anytime *E.coli* envelope transformants are pooled they will contain a plurality of envelope proteins. In other words anytime there is a pool of transformed cells that pool will comprise a plurality of structures.

Claim Rejections - 35 USC § 103

The rejection of claims 38-71, 73-76 and 78-94 under 35 U.S.C. 103(a) as being unpatentable over Gao et al. (Journal of Virology, 1996), Petropoulos et al. (Antimicrobial Agents and Chemotherapy, April 2000) in view of Grovit-Ferbas et al. (Journal of Virology, 1998) and Trkola et al. (Journal of Virology, 1999) **is maintained** for reason of record.

Applicants have indicated in their arguments that the term plurality can include both definition contemplated in the prior 112 second paragraph rejection above.

Applicants augments are that (1) there is no suggestion to combine the references (2) the combination of references must suggest to the ordinary artisan there is a reasonable expectation of success (3) that the combination of references does not teach or suggest every limitation of the rejected claims.

In response to applicant's argument (1) that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the Gao et al. reference teaches single round virus infectivity assays in which

PCR derived envelope clones from patient PBMC are inserted into a plasmid under the control of an HIV-long terminal repeat (see Gao et al. page 1654, column 1, starting at the 3rd paragraph). Viral particles (plurality of particles) are obtained by cotrasfecting the envelope containing plasmid with the *env*-deficient HIV provirus that contains the CAT indicator. The reference teaches the step of obtaining the particles that contain the viral nucleic acid lacking envelope but comprising an indicator and the particles also contain a plurality (of the same kind) of viral envelope proteins. These viral particles are then incubated with cells (PBMC) that express cell surface receptor to which the virus can bind. The infected cells are grown for several days before the CAT activity is measured. "The assay thus examines biosynthesis, transport, packaging, fusogenicity, and uncoating and scores positive only if the in *trans* complemented envelope glycoproteins perform all of these functions efficiently." (see Gao et al. page 1662, column 1, paragraph 2). The reference also indicates that the authors contemplated that the reagents taught in the paper can be used for the development and testing of HIV vaccines (see Gao et al. page 1665, column 1, last sentence). The ordinary artisan skilled in the art of HIV infectivity would know that the goal of a vaccine is to prevent viral infectivity by developing antibodies that can block the virus from entering the cell. The reference provides the motivation to add the additional step of including a test compound (such as an antibody) with the taught reagents. Therefore, the reference contemplates using the reagents in assays but does not actually perform such tests.

The Petropoulos et al. reference provides a similar particle production format as compared to the Gao et al. reference. A proviral vector in which the viral envelope has been replaced with an indicator, the provial vector is cotransfected into a cell with an envelope

expressing vector and the cell is incubated. The viral particles (plurality of viral particles) are produced and excreted into the supernatant and the plurality of particles is collected. The plurality of viral particles is then incubated with susceptible cells (those that express the necessary receptor) in the presence or absence of a compound. The production of the indicator is measured and the level of indicator is compared between cells treated with the compound and cells not treated the compound.

In response to applicants' argument (2) that the combination of references must suggest to the ordinary artisan there is a reasonable expectation of success. As discussed above the Gao et al. reference by itself suggests that the taught reagents would be useful for the development and testing of HIV vaccines. Therefore, the ordinary artisan would have had a high expectation of success in using the taught plurality of particles containing plurality of envelope proteins in assays that would test HIV vaccine candidates. "The assay thus examines biosynthesis, transport, packaging, fusogenicity, and uncoating and scores positive only if the in *trans* complemented envelope glycoproteins perform all of these functions efficiently." (see Gao et al. page 1662, column 1, paragraph 2). The ordinary artisan would have a high expectation of success in screening compounds that effect any of the following biosynthesis, transport, packaging, fusogenicity, and uncoating which would be measured by their effect on CAT activity. Based on the Gao et al. reference alone the ordinary artisan would have a high expectation of success in using the taught reagents for screening assays. The other references cited in the rejection further buttress the Gao et al. rejection because they teach the application of the basic scientific principle of screening compounds and set out the knowledge of the ordinary artisan at the time the invention was made.

In response to applicants arguments (3) that the combination of references does not teach or suggest every limitation of the rejected claims, it is not clear what limitation are not set out in the instant combination of refecnes.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants addressed each references and indicated that none of the references teach multiple envelope constructs.

It remains the position of the Office that the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made to test a patient derived HIV sample for the ability to be inhibited by a compound that will prevent viral entry. One having ordinary skill in the art would have been motivated to do this in order to screen potential vaccine candidate for their production of antibodies that can prevent viral entry into the cell as suggested by Gao et al. (see. page 1665, column 1, last sentence). It would have been obvious to one having ordinary skill in the art to monitor antiretroviral therapies in a patient by determining if the patient derived virus has mutated in such a way as to be resistant to the drug regime that the patient is being treated with. This information is clinically valuable by providing reliable assessment of the viral burden and is useful in monitor the clinical efficacy of the treatment. Gao et al. teach a single round infectivity assay that utilizes various patient derived and amplified env segments, the reference utilizes CAT as the indicator gene which is found on the resistance test vector which also comprises the ga*g/pol* gene sequences but has the *env* sequence deleted. The reference teaches that different *env* sequences have different biological characteristics. The env

clones can be utilized in envelope complementation and infectivity assays. Petropoulos et al. teach an assay for testing drug susceptibility, the assay utilizes a resistance test vector and a *env* vector for the production of viral particles from cotransfected cells. Grovit-Ferbas et al. teach that different viral envelope sequences have different effects on the ability of a viral particle to enter a host cell. Those viruses that have diminished capacity to enter a new host cell are found in long term HIV survivors, indicating that reducing the ability of a new particle to enter the next host cell will be beneficial for increasing the survival of an HIV infected person. The reference also teaches assaying each viral envelope sequence for the usage of different coreceptors. While the Trkola et al. reference teaches an assay that determines if an antibody is able to inhibit the entry of a viral particle into a new host cell, a use is suggested by Gao et al. (see. page 1665, column 1, last sentence). The prior art teaches assays that focus on the HIV viral envelope protein and indicate preventing viral entry by blocking the association of the viral envelope with the cell surface receptor is a desirable drug target. It is well established in the prior art that HIV has a high mutation rate, especially in the envelope region, hence vaccines have not been successful due to the changing envelope structure of the virus. The prior art also indicated that for any therapy to be effective it is necessary to assay the changes in the virus population in a patient and follow the mutations that occurs when applying drug therapy. This will ensure that the patient is treated with the best possible drug combination that is effective for the virus the patient harbors at any point. Therefore, the instant invention is obvious over Gao et al. and Petropoulos et al. in view of Grovit-Ferbas et al. and Trkola et al.

New rejection in view of applicants' amendments to the claims:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49, 50, 75, 79, 80 recites the limitation "the plurality of nucleic acids" in the dependent claims. There is insufficient antecedent basis for this limitation in the independent claim.

Claims 59, 60, 61, 62 and 64 recites the limitation "the plurality of cells" in the dependent claims. There is insufficient antecedent basis for this limitation in the independent claim that only makes reference to mixing viral particles with cells.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

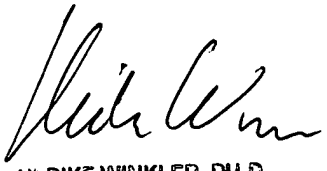
Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.



ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 9/4/05